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TABLE OF CONTENTS

INTRODUCTION

The major hypotheses to be tested in this project are that high-level occupational exposure of former capacitor workers to polychlorinated biphenyls (PCBs) will result in reductions in: (i) performance on neuropsychological and neurological tests that reflect the historic PCB body burden of the individual and (ii) the number of dopamine (DA) terminals in the basal ganglia.

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY, have undergone neuropsychological and neurological exams, completed a comprehensive occupational, residential and dietary questionnaire, had blood drawn to measure serum thyroid hormone and PCB concentrations, and undergone a non-invasive test to determine bone lead concentrations in Albany, NY. This latter measure will reduce the likelihood of confounding the neurological effects of prior PCB exposure with the neurological effects of prior lead exposure. Finally, approximately 40% of the subjects have participated in a second portion of the study that uses brain β-CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging took place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

In order to test the above hypotheses we have gathered a team of internationally recognized experts in the epidemiology of environmental and occupational exposure to PCBs, the neurology of movement disorders and Parkinson's Disease, the assessment of toxicant-induced deficits in neuropsychological function, measurement of serum PCB concentrations, non-invasive determination of bone lead concentrations, and brain imaging of central DA neurons and their relationship to movement disorders, including Parkinson's Disease.

STUDY INVESTIGATORS

Albany, NY Based Testing

Richard F. Seegal - Wadsworth Center, New York Sate Dept. of Health (NYSDOH): Principal Investigator

Edward F. Fitzgerald – University at Albany, School of Public Health: Epidemiologist

Lenore J. Gensburg - Center for Environmental Health, NYSDOH: Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

Eric S. Molho, Donald S. Higgins - Albany Medical Center: Neurological Assessment

Stewart A. Factor - Emory University: Neurology Consultant

Robert J. McCaffrey - University at Albany: Neuropsychological Assessment

Richard F. Haase - University at Albany: Biostatistician

Mary S. Wolff - Mount Sinai School of Medicine: Serum PCB Analyses

Andrew C. Todd - Mount Sinai School of Medicine: Bone Lead Determination

Patrick Parsons - Wadsworth Center, NYSDOH: Bone Lead Determination

New Haven, CT Based Testing

Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders: ß-CIT SPECT Brain Imaging

PROGRESS IN FISCAL YEAR 2006

The following narrative provides descriptions of the progress we have made in the fifth year of the project (fourth year of data collection)—a period in which we have been actively engaged in both data collection and analysis of the resulting data. At the conclusion of data collection in mid April 2006 we had tested 241 subjects in Albany which represents 97% of our projected goal of testing 248 subjects. In addition, 89 of those subjects traveled to New Haven, CT to undergo β-CIT imaging to estimate the density of basal ganglia dopamine transporters. This number represents 93% of our stated goal of testing 96 subjects. Given the distance of travel (2.5 hours) and the necessity of committing two days for the imaging, we are particularly proud of having almost reached this latter goal.

A significant effort has been, and continues to be made, to analyze the vast amounts of data that were generated during active data collection. In addition to collecting the major dependent variables (neurological, neuropsychological, β-CIT, bone lead, thyroid hormone and serum PCB concentrations) we have also collected extensive information from a 2-2.5h interview that will provide important information on potential confounders that may influence the dependent variable outcomes listed above. A list of these potential confounders that are currently being examined is included in Appendix 1.

Interview data pertaining to demographic characteristics, medical history, medication use, smoking and alcohol consumption and diet (including sport fish) and other relevant variables have been double data entered and subdivided into subject-specific SAS datasets. Edit programs have been developed to detect out-of-range and logical inconsistencies and any errors have been corrected. The occupational histories have been reviewed by two certified industrial hygienists who evaluated each job for the likelihood of exposure to PCBs, lead, mercury, and pesticides, using a four point scale. Each job has also been classified using Standard Industrial and Occupation codes and medications have been coded according to the American Hospital Formulary Service.

Table I provides information on the basis demographics of individuals who were contacted and asked to participate in the Capacitor Worker Study.

TABLE I: Albany, NY Testing, Participation of Potential Subjects at the End of Recruitment 4/19/06 (n=490)

	YES: 241		NO: 249	
GENDER				
Male	129	53.53%	104	41.77%
Female	112	46.47%	145	58.23%
AGE				
50s	91	37.76%	87	34.94%
60s	77	31.95%	67	26.91%
70s	59	24.48%	66	26.51%
80-90s	14	5.81%	29	11.65%

Following testing in Albany, subjects were asked if they wished to participate in the SPECT β-CIT imaging portion of the study carried out by Dr. Marek's group at the Institute for Neurodegenerative Disorders in New Haven, CT. Despite the fact that these procedures require a two day stay in New Haven and the injection of a radio-labeled tracer, we were able to test 93% of the subjects we had originally stated we would test. These data are presented in Table II.

TABLE II: New Haven, CT Testing, Participation of Potential Subjects at the End of Recruitment 8/31/06 (n=241)

	YES: 89		NO: 128		Not Contacted: 24	
GENDER						
Male	50	56.18%	67	52.34%	12	50.00%
Female	39	43.82%	61	47.66%	12	50.00%
AGE						
50s	34	38.20%	46	35.94%	11	45.83%
60s	38	42.70%	32	25.00%	7	29.17%
70s	13	14.61%	40	31.25%	6	25.00%
80-90s	4	4.49%	10	7.81%	0	0.00%

The lower participation rates of subjects in their 70s and 80s reflect the difficulties in both traveling to New Haven, CT and committing to a two night stay. We feel that participation rates would have been lower if we had not provided round-trip limousine service.

Table III presented below provides a summary of tracing, screening and recruitment for individuals through April 19, 2006. Tracing refers to the procedures carried out to identify and locate individuals who potentially could take part in the study, while screening refers to the procedures carried out by staff at the Center for Environmental Health (a part of the New York State Department of Health) to determine if the individuals were medically eligible. A list of conditions that made subjects medically ineligible is presented in Appendix 2. If eligible, the subjects' names were sent to the Study Coordinator who contacted them to more completely describe the test protocols and schedule their visits to Albany.

TABLE III: Subjects Selected from Cohort (n=6798) Through the End of Recruitment 4/19/06

Tracing Results	**Entered Tracing: 2920**	
Dead	885	30.31%
Out of Area	245	8.39%
Too Young	0	0.00%
Could not be Located	562	19.25%
Eligible for Screening	**1181**	**40.45%**
Not Traced	47	1.61%

Screening Results	**Entered Screening: 1181**	
Refused	232	19.64%
Ineligible-Medical	341	28.87%
Ineligible-Non-Medical	65	5.50%
Eligible for Recruitment	**491**	**41.57%**
Not Screened	52	4.40%

Albany Testing: Recruitment Results	**Entered Recruitment: 491**	
Participated	**241**	**49.08%**
Refused	249	50.71%
Remaining*	1	0.20%

New Haven Testing: Recruitment Results	**Entered Recruitment: 241**	
Participated + Scheduled (5)	**89**	**36.93%**
Refused	128	53.11%
Other**	24	9.96%

*Not scheduled as of the end of the study.
**Cancelled, ineligible, no contact, could not be scheduled.

Table IV provides a summary of the final subject participation in both the Albany, NY and New Haven, CT portions of the study from inception through 19 April 2006.

TABLE IV: Summary of Subject Participation at the End of Recruitment 4/19/06

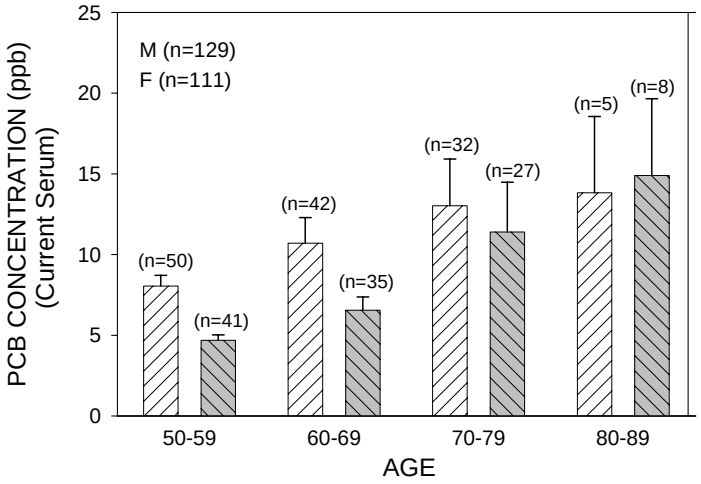
	All Subjects	
Albany Participation		
Yes, Participated	241	49%
Not Contacted	1	<1%
Refused	249	51%
TOTAL	**491**	**100%**
New Haven Participation		
Yes, Participated	89	37%
Scheduled/Not Tested	2	1%
Not Contacted	12	5%
Ineligible	5	2%
Cancelled	5	2%
Refused	128	53%
TOTAL	**241**	**100%**

Measurement of Serum PCB Concentrations

Dr. Mary Wolff, of the Mt. Sinai School of Medicine, has analyzed serum PCB concentrations from the former capacitor workers using glass capillary gas chromatographic techniques. Data includes not only congener specific determination of current serum PCB concentrations, obtained when the subjects traveled to Albany, but also, for those individuals for whom we have archived sera, re-analysis using the same analytical procedures described in the grant application. The availability of both current and archived sera PCB levels, determined in the same laboratory using the same analytical techniques, will allow us to more precisely estimate historic serum PCB levels for those individuals for whom we do not have archived sera.

The data presented below represents PCB analyses from 240 subjects broken down by age (decade) and gender. It is noteworthy that the serum PCB levels remain elevated (average PCB levels in non-occupationally-exposed individuals are approximately 2-3 ppb) more than twenty-five years after occupational exposure ceased. Although we chose to present only total PCB concentrations (a sum of lightly and heavily chlorinated congeners), subsequent analyses, particularly for levels of lightly chlorinated congeners that have short half-lives, will allow us to discriminate between occupational and more recent recreational and/or residential exposures.

Figure 1. Total Current Serum PCB Levels (mean ± sem)



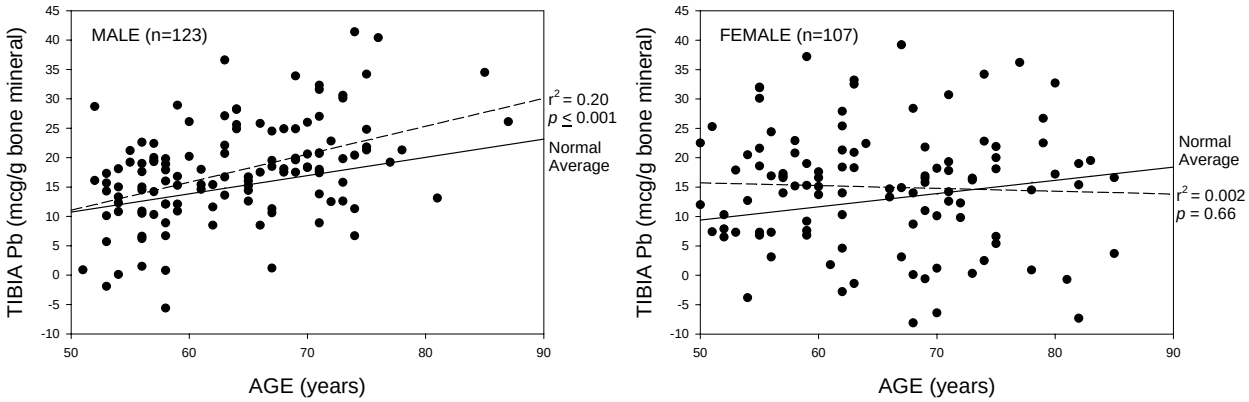
Measurement of Bone Lead Concentrations by K-Shell X-Ray Fluoresence

Dr. Andrew Todd of Mount Sinai supervised the *in vivo* measurement of lead in bone in Albany and analyzed the raw data (in electronic form) generated with the bone lead measurement system. Mount Sinai personnel also provided consultation on all aspects of the X-ray Fluorescence bone lead measurement system, including regular and *ad hoc* consultation, as required, on the quality of spectra acquired, the control and use of the measurement system and the reliability of the analytical results in order to provide both the most precise and the most reliable bone-lead data possible.

Mount Sinai personnel also supervised the Albany XRF operators in the daily operation of the XRF measurement system with regard to its maintenance, calibration, optimization and quality control protocol and have provided expertise on the optimization of the measurement system with regard to operational parameters of the spectroscopy electronics (*viz.* rise time, flat-top, *etc.*).

All calibration and human measurement XRF data have been electronically transmitted to the Mount Sinai XRF Laboratory for analysis. The analyses of the data received to date have been completed. Analyses of new data are being performed as they arrive. A total of 230 study participants have had their bone lead measured and analyzed; these bone lead data are presented in Figure 2 below and demonstrate a significant association between tibia lead concentrations in men, but not in women.

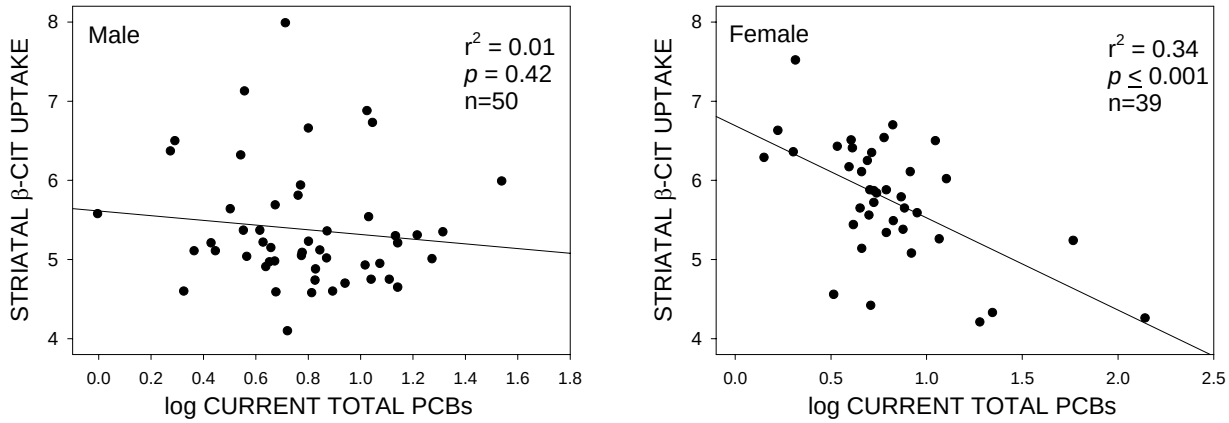
Figure 2. Tibia Lead (Pb) Concentrations by Age and Gender



Measurement of Brain Dopamine Transporter by β-CIT SPECT Imaging

Preliminary analysis of the data yielded a significant statistical relationship between dopamine transporter density measured by β-CIT SPECT imaging and current serum total PCB concentrations which was observed only in female former capacitor workers. This measurement represents the average uptake of the radio-labeled ligand [^{123}I]β-CIT in the putamen and caudate of male and female former exposed workers measured by SPECT imaging, providing an *in*-vivo measure of dopamine transporter density. Total PCB levels were measured in serum from the subjects at the time of imaging. The significant negative relationship seen only in female workers—all who were postmenopausal—has allowed us to formulate a hypothesis that estrogen withdrawal increases risk of basal ganglia dopamine dysfunction only in women (see also Conclusion). As noted in Appendix 3 this gender difference remains when age was controlled for statistically.

Figure 3. Dopamine Terminal Density Measured by β-CIT SPECT Imaging as a Function of Current Serum PCB Concentrations



Measurement of Serum Thyroid Hormone Function

Analysis of serum samples collected for thyroid hormone function (T_3, T_4, free T_3, free T_4, and TSH levels) has been conducted by the Clinical Chemistry group of the Clinical Laboratory Evaluation Program of the New York Sate Department of Health. A total 155 serum samples were collected and analyzed for thyroid hormone function. These data, summarized by gender, are presented in Table V. Preliminary examination indicates that the data falls within the normal ranges for these measures.

TABLE V: Thyroid Hormone Level in Serum

Thyroid Hormone Measure	Male (N=73)		Female (N=82)	
	Mean	sem	Mean	sem
TSH	2.06	0.13	2.55	0.36
T4	7.94	0.18	8.72	0.22
Free T4	1.23	0.02	1.22	0.03
T3	133	3.05	122	2.74
FreeT3	5.31	0.08	4.56	0.08

TSH = Thyroid Stimulating Hormone
T4 = Thyroxine
T3 = 3,5,3-Triidothyronine

Investigators Meetings and Communication with Participants

In order to facilitate communication between researchers who are located at the different institutions in Albany, we have met quarterly during the past year. These meetings have proven to be extremely useful and allow us to avoid many of the pitfalls that might otherwise occur in the conduct of this complicated multi-institutional epidemiological study. Topics discussed included modifications to phone screening to include chemotherapy and radiation questions, revisions to reproductive section of the interview form to include definitive age at menopause and hormone replacement therapy. In early June 2006 a meeting of all investigators (including Drs. Marek and Korrick) was held in Albany to present preliminary results and plan strategies for data analyses.

Drs. Fitzgerald (our epidemiologist), Haase (our statistician) and Seegal (Principle Investigator) now meet bi-weekly to review ongoing progress, present analyses of data and plan the writing of manuscripts.

KEY RESEARCH ACCOMPLISHMENTS

As in all epidemiological studies, presentation of results prior to controlling for potential confounders (*e.g.,* age, gender, life style [smoking, alcohol and drug use], and medications) that may affect the dependent variables of interest (*i.e.,* neurological, brain imaging, neuropsychological measures) is premature. Hence, the dependent variables described above are prior to statistical control for potential confounders. We present, however, in Appendix 3 a preliminary statistical comparison of the relationships between current serum PCB concentrations and β-CIT for men and women in which age is treated as a quasi-confounder. These statistical comparisons strongly suggest that gender, not age, is a major factor in influencing the PCB x β-CIT relationship and illustrate the logical and statistical procedures we will employ in the coming year to analyze the relationships between exposure to PCBs and other major dependent variables.

REPORTABLE OUTCOMES

In March 2006 I presented a seminar at the University of Iowa, Iowa City, IA, entitled 'PCB-Induced Neurodegeneration: Altered Dopamine Storage and Oxidative Stress'. A majority of that presentation was based on laboratory data derived from experiments that were heavily influenced by the Capacitor Worker Study.

We anticipate a series of five publications summarizing the major findings of the project. The first publication will examine associations between serum PCB concentrations and occupational exposure as well as fish consumption. The senior author of this manuscript will be Dr. Edward Fitzgerald who has begun writing the manuscript.

The second publication will focus on whether current serum PCB levels can be used to accurately predict concentrations in 1976, using half life models developed from that subset of persons who have serum PCB determinations at both time points. The models derived from this analysis would then be used to estimate 1976 PCB body burdens for the entire study population. The writing of this manuscript will be headed by Drs. Seegal and Wolff.

Three additional publications will address the association between both current and estimated historical serum PCB levels and the major health endpoints of the study; (1) neurological, (2) neuropsychological, and (3) β-CIT. We anticipate that the appropriate co-investigators will serve as senior authors for these manuscripts. We expect that all five manuscripts will be completed within the next eighteen months.

CONCLUSIONS

For the fourth and final year of data collection we have come very close to our originally stated goals for recruiting and testing subjects, both in Albany, NY and in New Haven, CT. We are proud of this progress since many of our subjects are elderly and must travel considerable distances to undergo testing at these two sites.

We have completed data collection and have begun careful review of the data to determine initial trends. For example, interim data analyses have demonstrated a highly significant negative correlation between current PCB serum concentrations and β-CIT SPECT imaging of dopamine transporter density in the caudate/putamen that is only seen in women. This unexpected finding is supported by a recent publication by Steenland *et al.* (*Epidemiology* **17**(1), 8-13, 2006) that demonstrated increased Parkinson's disease mortality only in female former capacitor workers.

A discussion of the statistical procedures used to determine the relationships between PCB levels, age and gender and β-CIT is presented in Appendix 3. We are particularly excited with these preliminary statistical analyses that demonstrate that, although β-CIT decreases with age while PCB concentrations increase with age, there is a significant gender x PCB interaction. This finding not only supports the epidemiological findings of Steenland *et al.* 2006), but also supports our original hypothesis that, in a manner similar to that seen in PCB-exposed adult non-human primates, PCBs reduce dopamine function in the basal ganglia. Indeed, these findings led to the successful awarding of an NIH grant to Seegal to study the role of gender and ovarian hormones in influencing PCB-induced changes in brain dopamine function.

We continue to show that current serum PCB levels are significantly elevated in former capacitor workers compared to literature values for non-occupationally exposed individuals. These findings demonstrate, given the many years since occupational exposure ceased, the extraordinarily high levels of PCBs to which these workers had been exposed.

Finally, we are analyzing sera to determine whether occupational exposure has altered thyroid hormone function in these workers. We will use that information to statistically determine the contributions of endocrine disruption, in addition to those hypothesized to occur following reductions in central dopamine function on neurological, neurobehavioral and imaging outcomes.

APPENDICES

Appendix 1: List of Potential Confounders

Appendix 2: Medical Questions from Screening Questionnaire

Appendix 3: An Illustration of Statistical Procedures to Control for Quasi-Confounders in Understanding the Relationship between Serum PCBs and β-CIT Imaging

APPENDIX 1

List of Potential Confounders

Medical Conditions (ever told by MD)
High blood pressure
Diabetes
Thyroid Disease
Prior neurological condition
Other medical conditions
Arthritis
Carpal tunnel syndrome
Other muscle or joint condition

Medications (last two yrs)
Cardio meds
Antibiotics
Ca channel blockers
Gout meds
Sex hormones
Diuretics
Anti-depressants
Beta blockers
Diabetes meds
Acetaminophen
Potassium supplement
Gastro-intestinals
Ace inhibitors
Hyperlipoproteinemia meds
Thyroid meds

Age
Gender
Education
IQ
Body Mass Index
Marital status
Smoking
Drinking
Physical activity level
Hours of sleep per night
Employment status (yes/no)
Exposure to lead, mercury, solvents, or pesticides from job or hobbies
Caffeine

APPENDIX 2

Medical Questions from Screening Questionnaire

3. I need to ask you some questions about your medical history. Your answers will be kept strictly confidential.
Without identifying the disease or condition by name, could you please tell me if **you** have ever been diagnosed or treated by a doctor for any of the following conditions or diseases?

Please wait until the end of the list to give me your answer.

- Multiple sclerosis
- Stroke resulting in a hospital admission
- Brain surgery
- HIV/AIDS
- Hospitalization for depression or other emotional problems in the past one year

Yes ___ No ___ Don't know ___ No Response ___

4. I am going to read you two more lists to ask about some other medical conditions and habits. Again, *without identifying the condition by name*, could you please tell me if any of the following conditions or treatments apply to **you**?

Please wait until the end of the lists to give me your answer.

Do you currently:
- Abuse Drugs or
- Consume 5 or more drinks of alcohol per day

Or Have you ever had:
- A head injury resulting in a concussion diagnosed by a doctor, head injury resulting in loss of consciousness, or head injury resulting in confusion;
- nervous system radiation (such as for brain or spinal cord cancer); or
- chemotherapy

Yes ___ No ___ Don't know ___ No Response ___

5. Next I will read a list of medical conditions to you. Can you please tell me if currently or in the past 6 months you have been treated with any drugs for the following conditions?
Please wait until the end of the list to give me your answer.

- Psychoses / seeing, hearing or feeling things that are not there
- Epileptic seizures
- Depression / sadness
- Anxiety / nerves
- Shortness of breath

Yes ___ No ___ Don't know ___ No Response ___

APPENDIX 3

An Illustration of Statistical Procedures to Control for Quasi-Confounders in Understanding the Relationship between Serum PCBs and β-CIT SPECT Imaging

Preliminary Evaluation of the PCB→β-CIT Relationship for Men and Women

It is best not to analyze the two groups separately, mainly because of loss of power due to the small N for the women (n=39), and similar statistical power problems for separate analyses performed on the men alone (n = 50). It is a more powerful strategy to keep the whole sample intact and address the same issues of within-group relationships by way of interactions and simple main effects, thus preserving the error degrees of freedom at a higher value (89-*k*-1; *k* = number of vectors in the problem), and allowing for more powerful tests of the hypotheses.

The Gender by PCB Model with Interaction

The 2 (gender) by 1 (log total PCB) general linear model "factorial", yielding main effects for gender and total PCBs, as well as the gender*PCB interaction:

Table 1: 2 x 1 General Linear Model "factorial"

Tests of Between-Subjects Effects

Dependent Variable: beta_cit

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	10.490[b]	3	3.497	7.121	.000	.201
Intercept	490.923	1	490.923	999.736	.000	.922
gender	3.724	1	3.724	7.585	.007	.082
log_totpcb	5.100	1	5.100	10.385	.002	.109
gender * log_totpcb	1.776	1	1.776	3.616	.061	.041
Error	41.740	85	.491			
Total	2789.414	89				
Corrected Total	52.230	88				

a. Computed using alpha = .05

b. R Squared = .201 (Adjusted R Squared = .173)

Note that the interaction is significant enough to catch your attention (p = .061), especially with a small sample (n = 89) and an effect size based on a partial η^2 = .041, which is a very typical magnitude of effect in the social and behavioral sciences. In group contrast terms, an η^2 of .041 is equivalent to mean difference of slightly less than ½ a standard deviation (Cohen's *d* = .413).

The Gender by PCB Simple Main Effects Model

The simple main effects model of the same analysis allows us to investigate the decomposition of the sums of squares within each group (men and women). The PCB main effect and the PCB*gender interaction of Table 1 is reconstituted as two simple main effects: the PCB→β-CIT relationship within the males in the sample, and the PCB→β-CIT relationship within females in the sample. The GLM source table includes the main effect for gender, and the two simple main effects:

Table 2. The gender by PCB simple main effects analysis

Tests of Between-Subjects Effects

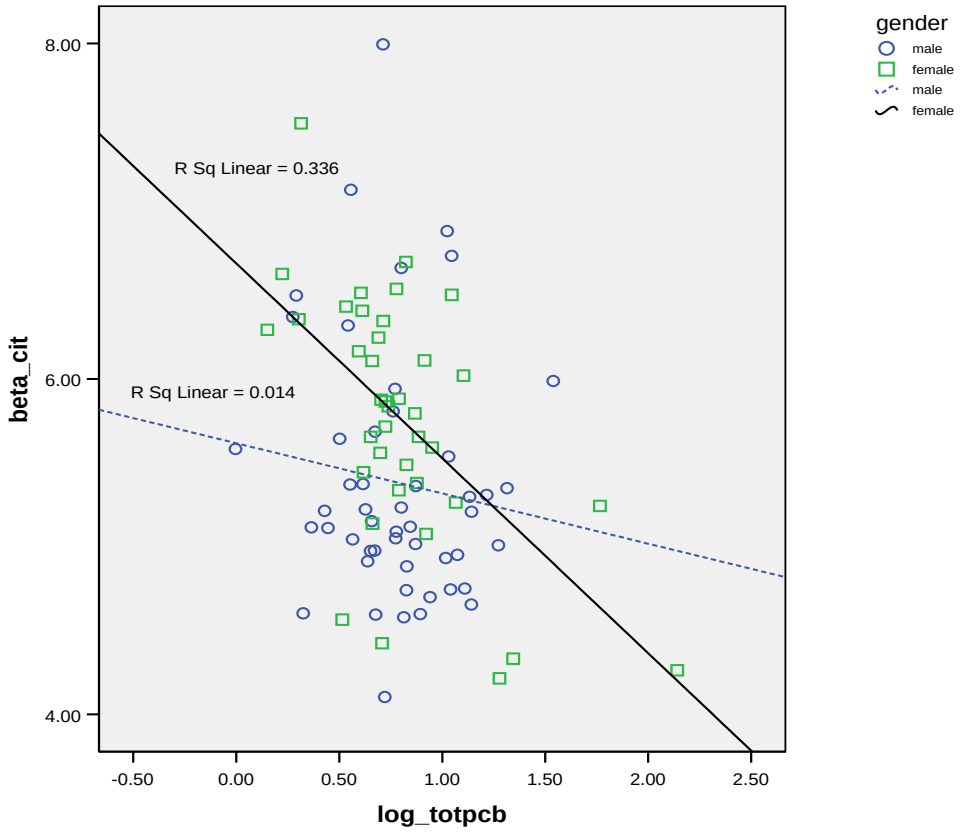
Dependent Variable: beta_cit

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	10.490[b]	3	3.497	7.121	.000	.201
Intercept	490.923	1	490.923	999.736	.000	.922
gender	3.724	1	3.724	7.585	.007	.082
logtot_w_male	***.395***	***1***	***.395***	***.805***	***.372***	***.009***
logtot_w_female	***7.034***	***1***	***7.034***	***14.325***	***.00029***	***.144***
Error	41.740	85	.491			
Total	2789.414	89				
Corrected Total	52.230	88				

a. Computed using alpha = .05

b. R Squared = .201 (Adjusted R Squared = .173)

The explanation for the sizable interaction observed in the analysis of Table 1 is that the effect of PCBs on β-CIT among women is very substantial (14.4% of the variability in β-CIT) and highly significant (p = .00029), but virtually nonexistent among the men. Note that the error degrees of freedom in each of these analyses is 85—substantially more powerful statistically than would have been the case of $df_e = 37$ or $df_e = 48$ had the analyses been performed separately.



Alternative Explanations for the PCB→β-CIT Relationship: Potential Confounds

In order to assert that the PCB→β-CIT relationship is not spurious, we must adjust for (eliminate) the variance in the dopamine transporter variable that may be accounted for by other plausible confounds, including age, medical history, current health status, pharmaceuticals, and so forth. The one potential confound that is available to us at the moment is age. The age adjusted, gender by PCB simple main effects analysis is presented in Table 3.

Table 3. Age adjusted Gender by PCB Simple Main Effects Analysis

Tests of Between-Subjects Effects

Dependent Variable: beta_cit

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	13.589[b]	4	3.397	7.385	.000	.260
Intercept	64.766	1	64.766	140.793	.000	.626
age	3.099	1	3.099	6.736	.011	.074
gender	1.808	1	1.808	3.930	.051	.045
logtot_w_male	***.576***	***1***	***.576***	***1.252***	***.266***	***.015***
logtot_w_female	***2.666***	***1***	***2.666***	***5.795***	***.018***	***.065***
Error	38.641	84	.460			
Total	2789.414	89				
Corrected Total	52.230	88				

a. Computed using alpha = .05

b. R Squared = .260 (Adjusted R Squared = .225)

Even after adjusting for age, the relationship between PCB→β-CIT remains statistically significant and possesses a measure of association ($\eta^2 = .065$) that is substantial when compared to the typical effect sizes in both medicine and the behavioral sciences.

We now need to think carefully about, and then to add to this model, the remaining plausible confounds or 3rd variables—if the PCB→β-CIT relationships can survive our attempts to make it vanish by assessing adding additional confounds, then there may well be something here worth reporting. In order to be considered a confound the potential 3rd variable must (1) be correlated to PCBs, (2) be correlated to PCB→β-CIT, and must have logical grounds for being seen as the mechanism that accounts for a spurious PCB→ PCB→β-CIT relationship.

As a final note, it could be argued that age is not a confound, but is a pseudo-confound—that is, age belongs on the causal pathway to both PCBs and β-CIT in a model in which PCB is *both* a dependent and independent mediating variable between age and β-CIT. In this fashion both direct and indirect effects of age can be assessed and we would not eradicate a certain portion of the "confounded" covariance of the Age→PCB relationship.